REMARKS

Claims 22-44 are pending in this application. Claim 24 has been rejected under 35 U.S.C. § 112, first paragraph, for overbreadth. Claims 22-44 are rejected under 35 U.S.C. § 112, second paragraph, for lack of clarity. Claims 22-23, 25-30, and 32-41 are rejected under 35 U.S.C. § 102(b) for anticipation over Gerhart et al. (U.S. Patent No. 5,085,861; hereinafter "Gerhart"). Claims 22-44 are rejected under 35 U.S.C. § 103(a) for obviousness over Kossovsky et al. (U.S. Patent No. 5,462,751; hereinafter "Kossovsky") in view of Constantz et al. (U.S. Patent No. 5,782,971; hereinafter "Constantz"), Relyveld (U.S. Patent No. 4,016,252; hereinafter "Relyveld"), and Gupta et al. (Vaccine Design, Chapter 8, pp. 229-248, 1995; hereinafter "Gupta"). Claims 22-44 are provisionally rejected for obviousness-type double patenting over claims 22-44 of copending U.S. Serial No. 09/692,664. By this reply, Applicants amend claims 22, 24, 40, and 42 and address the Examiner's rejections below.

Support for the Amendment

Support for the amendment to claims 22, 24, 40, and 42 can be found in the specification on, for example, page 6, lines 21-25, and the claims as originally filed. No new matter is added by the amendment.

Priority

The Examiner states that to obtain the benefit of an earlier priority date, the application must contain a specific reference to the prior application in the first sentence of the specification or in an application data sheet (37 C.F.R. § 1.78(a)(2) and (a)(5)). The Examiner has not clearly

indicated whether Applicants' claim for priority has been acknowledged or rejected. Applicants submit that the first paragraph of the application and the application data sheet (a copy of which is provided herewith) as filed on October 20, 2000 contained the following priority data:

--Cross Reference To Related Applications

> This application is a continuation-in-part application of U.S.S.N. 09/153,133, filed September 15, 1998 entitled "Calcium Phosphate Delivery Vehicle and Adjuvant," the contents of which are incorporated by reference.
> This application also is a continuation-in-part application of U.S.S.N. 08/729,342, filed October 16, 1996, entitled "Delivery Vehicle," the contents of which are incorporated by reference.--

Therefore, the appropriate claim to priority has been made and Applicants respectfully request acknowledgment of the priority claim.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejects claim 24 under 35 U.S.C. § 112, first paragraph, for overbreadth. The Examiner states that "[t]he recitation of 'derivatives thereof' in claim 24 directs the claim to encompass a plethora of compounds, the scope of which is not enabled. Specifically determining the toxicity and efficacy of all such compounds for *in vivo* use require[s] undue experimentation." (Office Action, p. 3-4.) Applicants respectfully disagree.

Applicants have amended claim 22, from which claim 24 depends, to remove the phrase "a physiologically effective amount of." Accordingly, claim 24 no longer requires that any particular amount of the anticancer component be present in the claimed composition.

Applicants point out that claim 24, as amended, is directed to a composition comprising a calcium phosphate paste and an anticancer agent, or derivative thereof, selected from the list

provided, as well as mixtures thereof. All that is required to practice the claimed invention is the ability to mix the two components together. The claim does not require that the composition actually treats the tumor. Therefore, the specification does not need to provide a specific protocol to "prove the efficacy of the presently claimed composition in eliciting the desired response," as is stated by the Examiner (Office Action, p. 3). Claim 24 is a composition claim, not a method claim, and does not require that any particular physiological response be obtained, only that the two components can be mixed together to form the claimed composition.

The Examiner also states that "[t]he specification does not provide guidance as to how one skilled in the art would go about selecting a derivative of choice in forming the instant compositions." The listed anticancer agents are well known in the field and the process of generating derivatives of these agents is well within the purview of a skilled artisan. Therefore, the act of selecting a derivative would be a matter of choice. A determination of whether the derivative exhibited anticancer activity would be simply a matter of routine experimentation.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 22-44 under 35 U.S.C. § 112, second paragraph, for lack of clarity. The Examiner asserts that the use of the term "poorly" in claims 22, 27, 30, and 33 renders the claim indefinite. Applicants respectfully traverse this rejection.

The Examiner states that "[t]he term 'poorly' is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." Applicants direct the Examiner to page 9, lines 19-25 of the specification, which clearly provides a detailed definition

for the term "poorly crystalline apatitic (PCA) calcium phosphate." This definition defines PCA calcium phosphate as "a synthetic calcium phosphate of apatitic structure demonstrating only short-range crystallinity." The PCA calcium phosphate is further defined as "demonstrat[ing] the characteristic X-ray diffraction pattern of an apatitic mineral, namely two broad peaks in the region of 20-35° with a peak centered at 26° and a second peak centered at 32°." One skilled in the art, upon reading this definition, would reasonably understand what was meant by the term "poorly crystalline apatitic calcium phosphate." Thus, the term is clearly defined in the specification and the indefiniteness rejection of these claims should be withdrawn.

The Examiner also rejects claim 24 for reciting "derivatives thereof." The Examiner states that this term encompasses "various possible moieties, the metes and bounds of which are not clear" and that the "individual compound of claim 24 can contain numerous functional or non-functional derivatives." The Examiner thus asserts that this term renders claim 24 indefinite. Applicants respectfully disagree.

As is discussed above, claim 24 is directed to a composition comprising two components, a calcium phosphate paste and an anticancer agent or a derivative thereof, selected from the list provided, as well as mixtures thereof. Derivatives of known compounds are easily identified by the skilled artisan. Furthermore, it is not necessary that each and every derivative exhibit anticancer activity. (See M.P.E.P. § 2164.08(b); The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled.)

The Examiner also rejects claim 40 for reciting "anticancer therapy" that "prevent[s] a decrease in tumor mass," which is contrary to the meaning of the term. Applicants have amended claim 40 to clarify the claimed subject matter. The claim now reads that the anticancer

therapy "promotes" a decrease in tumor mass, which is consistent with the ordinary meaning of the term.

Rejections under 35 U.S.C. § 102(b)

Claims 22-23, 25-30, and 32-41 stand rejected under 35 U.S.C. § 102(b) for anticipation over Gerhart. The Examiner states that:

> Gerhart disclose[s] calcium phosphate containing compositions comprising biocompatible calcium phosphate ceramics that can be in the form of an injectable or moldable paste and will solidify within 10 minutes after administration...Gerhard's compositions contain active agents that are readily used in the treatment of cancers such as bone tumor. (Office Action, p. 4.)

Applicants respectfully traverse this rejection.

The M.P.E.P. § 2131 states:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. Of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Gerhard discloses a "bone cement...comprised of a particulate biocompatible calcium phosphate ceramic and particulate resorbable calcium salt dispersed in a cross-linked biodegradable polyester matrix...[that can be] used for bone/implant fixation, or as a filler or cement for bone repair." (See the Abstract.) Gerhard also discloses that a pharmaceutical agent can be incorporated into the cross-linked biodegradable matrix (see col. 4, lines 30-34). Gerhard later describes the pharmaceutical agent as an antibiotic, e.g., gentamicin or vancomycin (see col. 10, lines 48-54). Gerhard fails to teach that the pharmaceutical agent is an anticancer agent.

The Examiner asserts that Gerhard discloses the treatment of cancers (i.e., bone tumors) using the presently claimed composition. Gerhard merely states that "the surgical cement...can...be employed...in the treatment of bone tumors. Such treatment typically involves excision of the tumor as well as portions of the surrounding bone, leaving a large cavity in the bone..." (See col. 13, lines 45-49.) Gerhard continues, stating that the cavity can be filled using synthetic bone substitutes (e.g., hydroxyapatite (HA) and tricalcium phosphate (TCP; see col. 14, lines 1-6). Gerhard fails to disclose that the treatment includes the use of an injectable or formable calcium phosphate paste that also contains an anticancer agent. Absent this teaching, Gerhard fails to provide each and every element recited in the present claims. Accordingly, Gerhard fails to anticipate claims 22-23, 25-30, and 32-41. For this reason, Applicants respectfully request that the rejection of claims 22-23, 25-30, and 32-41 under 35 U.S.C. § 102(b) over Gerhart be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 22-44 stand rejected under 35 U.S.C. § 103(a) for obviousness over Kossovsky in view of Constantz, Relyveld, and Gupta. The Examiner states that:

> [I]t would have been obvious to one of ordinary skill in the art at the time of [the] invention to modify concentrations and calcium phosphate ratios of Kossovsky to suitable parameters, as suggested by Constantz, Relyveld, and Gupta...[and] [f]urthermore, one of ordinary skill in the art would have been motivated to incorporate a second adjuvant, separately, as taught by Gupta; or in the form of a coating, as taught by Kossovsky's patent, to enhance the therapeutic efficacy of [the] calcium phosphate containing therapeutic composition.

Applicants respectfully traverse this rejection.

The M.P.E.P. § 2143.03 states "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)." Kossovsky merely describes a composition comprising biodegradable core particles that are coated with a layer that is designed to allow attachment of biologically active agents without denaturing them (see lines 1-4 of the Abstract). Kossovsky fails to teach or suggest a composition comprising a calcium phosphate paste and an anticancer agent. On the contrary, the Kossovsky composition consists of biodegradable core particles composed of crystalline calcium phosphate (brushite) that can be synthesized at a nanomeric size (between approximately 5 nm and 150 nm). Kossovsky discloses that the core particles can be used as a drug delivery system because the particles are small enough to avoid uptake by the Reticulo-Endothelial System (RES) of the body and can deliver the drug or biologically active agent *in vivo* without non-specific toxicity or loss of drug to macrophages (see col. 3, lines 57-67).

The Examiner also states that the Kossovsky composition can be modified to contain an anticancer agent, such as taxol (see, e.g., Example 16 of Kossovsky). Kossovsky merely states that taxol can be bound to the surface of the brushite particles. As is discussed above, the Kossovsky particles are not equivalent to the presently claimed calcium phosphate paste, therefore, even if the Kossovsky material were modified to include taxol, Kossovsky does not teach or suggest all of the limitations of the present claims.

Furthermore, contrary to the Examiner's assertion, the Kossovsky composition (i.e., particles) cannot be modified to yield the presently claimed calcium phosphate paste composition. The M.P.E.P. § 2143.01 explicitly states that "[i]f the proposed modification or

combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)..." Kossovsky discloses particles that "may be synthesized at a nanomeric size (between approximately 5 nm and 150 nm)" and that the small size "allows...drug delivery [without] uptake by the Reticulo-Endothelial System (RES) of the body...non-specific toxicity or loss of drug to macrophages." See col. 3, lines 57-67. Thus, the advantage of the Kossovsky composition is that it provides dispersed carrier particles for use *in vivo* and *in vitro* as a drug delivery system that can avoid uptake and expulsion by the body. This advantage is realized only if the particles remain small and dispersable.

Present claim 22, in contrast, recites a composition comprising an anticancer agent and a calcium phosphate paste such that the paste has an injectable or formable consistency at the time of administration and is hardenable at the tumor site. Kossovsky fails to teach or suggest that the nanomeric particles can be provided as a paste, that they have a formable consistency, or that they are hardenable at the site of application. In fact, modifying Kossovsky to yield a hardenable paste would be contrary to the disclosure of Kossovsky, which clearly indicates that the particles, when administered, should be dispersed into the body (see col. 3, lines 57-67). Therefore, modifying Kossovsky to yield the present invention would change the principle of operation (i.e., modifying a dispersable particle to yield a hardenable paste), because it would negate the advantage of the Kossovsky particle (i.e., the ability to disperse throughout the body when administered). Accordingly, Kossovsky cannot be used to render the present claims obvious.

Constantz, Relyveld, and Gupta do not Remedy the Deficiencies of Kossovsky

The Examiner relies on Constantz, Relyveld, and Gupta to provide support for the modification of Kossovsky to yield the present invention. Like Kossovsky, none of Constantz, Relyveld, or Gupta teach or suggest a composition comprising a calcium phosphate paste and an anticancer agent.

Constantz merely discloses a calcium phosphate cement composition that may contain, for example, an antibiotic or a protein (see, e.g., col. 5, line 57, though col. 6, line 11). Constantz fails to teach or suggest the addition of an anticancer agent. Relyveld describes a calcium phosphate gel that is useful for the preparation of adsorbed vaccines. Gupta simply describes the use of aluminum and calcium compounds as adjuvants for vaccines. None of these references teach or suggest the preparation of a calcium phosphate paste containing an anticancer agent that has an injectable or formable consistency at the time of administration and that is hardenable at a tumor site, as is recited in present claim 22.

The Examiner also states that, based on the combination of Kossovsky, Constantz, Relyveld, and Gupta, "the ordinary artisan would have had a reasonable expectation of success in preparing a ready to use kit for easing the access and use of such compositions at a clinical setting. This statement is directed to claim 42, which recites a kit for use in preparing a flowable anticancer composition. Applicants submit that for the reasons provided above, none of these references teach or suggest all of the claim limitations of claim 42, and claims dependent therefrom. Accordingly this rejection should be withdrawn.

Because the combination of Constantz, Relyveld, and Gupta with Kossovsky fails to teach or suggest all of the claim limitations, as is discussed above, Applicants respectfully

request that the rejection of claims 22-44 under 35 U.S.C. § 103(a) be withdrawn.

Provisional Obviousness-Type Double Patenting Rejection

The Examiner provisionally rejects claims 22-44 for obviousness-type double patenting over claims 22-44 of copending Application Serial No. 09/692,664, stating that:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because both claimed inventions are directed towards compositions comprising calcium phosphate and an anticancer agent. Office Action, p. 9.

In response to the provisional double patenting rejection of claims 22-44 over claims 22-44 of copending Application Serial No. 09/692,664, Applicants will submit a terminal disclaimer, if necessary, to overcome the rejection once otherwise allowable subject matter has been determined.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for three months, to and including February 27, 2003. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: Feb. 24, 2003

Paul T. Clark
Reg. No. 30,162

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

F:\04712\04712.027002 Reply to 08.27.02 OA.wpd

Version with Markings to Show Changes Made

In the claims:

A marked-up version of claims 22, 24, 40, and 42 is presented below.

22. (Amended) An anticancer composition comprising a mixture of [a physiologically effective amount of] an anticancer agent and a calcium phosphate paste, said paste comprised of one or more nanocrystalline or poorly crystalline calcium phosphates [phosphate] and a physiologically acceptable fluid, the paste having an injectable or formable consistency at the time of administration and hardenable at the tumor site.

24. (Twice Amended) The composition of claim 22, wherein the anticancer agent is selected from the group consisting of methotrexate, cisplatin, prednisone, hydroxyprogesterone, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, testosterone propionate, fluoxymesterone, vinblastine, vincristine, vindesine, daunorubicin, doxorubicin, hydroxyurea, procarbazine, aminoglutethimide, mechlorethamine, cyclophosphamide, melphalan, uracil mustard, chlorambucil, busulfan, carmustine, lomustine, dacarbazine (DTIC, dimethyltriazenomideazolecarboxamide), procarbozine, 5-fluorouracil, cytarabine, cytosine arabinoside, 6-mercaptopurine, tamoxifen, paclitaxel, etoposide, vinorelbine, gemcitabine, leuprolide, flutamide, goserelin acetate, thioguanine, and their derivatives and mixtures thereof.

40. (Amended) The composition of claim 22, wherein delivery of the anticancer therapy to the tumor site is sufficient to promote [prevent] a decrease in tumor mass without significant weight loss in the mammal.

42. (Amended) A kit for use in preparing a flowable anticancer composition that remains [remain] injectable for at least about 20 minutes, said kit comprising:

(a) dry ingredients comprising a nanocrystalline or poorly crystalline calcium phosphate and a second calcium phosphate in a proportion of about 1:10 to 10:1 by weight;

(b) a physiologically acceptable aqueous lubricant in an amount sufficient to produce a flowable product upon combination with said dry ingredients; and

(c) an anticancer agent in an amount ranging from about 0.01 to 10 wt. % of said dry ingredients.